

**National Children's Study
Federal Advisory Committee 23rd Meeting
January 14, 2010
Natcher Conference Center, National Institutes of Health
Bethesda, MD**

This meeting was held in conjunction with the National Children's Study (the Study), which is led by a consortium of federal partners: the U.S. Department of Health and Human Services (HHS) (including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD] and the National Institute of Environmental Health Sciences [NIEHS]) of the National Institutes of Health [NIH] and the Centers for Disease Control and Prevention [CDC]), and the U.S. Environmental Protection Agency (EPA).

Welcome from the Chair of the National Children's Study Federal Advisory Committee (NCSAC)

Alan R. Fleischman, M.D., NCSAC Chair; Senior Vice President and Medical Director, March of Dimes

Dr. Fleischman welcomed participants to the 23rd NCSAC meeting. He explained that the NCSAC will address a number of previously provided questions in the meeting's discussion sessions.

The Federal Advisory Committee Act (PL 92-463; passed on October 6, 1972) created standard and uniform procedures governing the operation of all federal advisory committees. The Act allows the federal government to obtain advice for long-range planning and development of programs from groups of outside experts through the formation of advisory committees. Under its charter, the NCSAC:

- Provides specific advice and recommendations to the NIH Director, NICHD Director, and the Study Director, regarding general direction and conduct of the Study, ethical concerns, community engagement and consideration, and hypotheses and other considerations of the Study
- Responds to specific requests for advice and recommendations
- Provides a forum for considering requests from the public and scientific community and provides opportunities for advocacy and industry perspectives and representation.

Dr. Fleischman reviewed the minutes from the October 21, 2009, NCSAC meeting, which included the following:

- Study update
 - Change in leadership and organizational responsibilities
 - Vanguard Study and the Main Study have different cohorts and different goals
 - The purpose of the Vanguard Study is to assess the feasibility, acceptability, and cost of Study recruitment, logistics and operations, and visits and visit assessments.
- Interagency Coordinating Committee (ICC) report
 - Each lead agency (NICHD, NIEHS, CDC, and EPA) has an essential role to play in the Study and will ensure that the Study plays a role in fulfilling each agency's mission

- Recruitment strategies
- Vanguard Study logistics
- Visit assessments
- Vanguard Center protocol.

National Children's Study Update

Steven Hirschfeld, M.D., Ph.D., Acting Director, National Children's Study, NICHD, NIH, HHS

Dr. Hirschfeld noted that the NCSAC will convene every 90 days in order to maintain as transparent an operation as feasible, to ensure that the Study is receiving the highest quality advice as possible, and to ensure that the NCSAC and the public are regularly kept informed of the Study's status. Therefore, the Study updates are a dynamic activity.

Study Description, Goals, and Structure. The Study is a congressionally mandated activity coordinated among federal agencies that include the CDC, the EPA, and the NIH, with the NIEHS contributing and the NICHD serving as the program lead. The Study is a large multicomponent, multiyear longitudinal study that is unprecedented in scope and complexity and therefore necessitates a planning process that is systematic, dynamic, flexible, and evidence based. The Study will examine the multiple effects of broadly defined environmental influences on the health and development of 100,000 children across the United States, following them from before birth until age 21, by providing high quality data to analyze scientific hypotheses. The overall goal of the Study is to improve the health and well-being of children. The Study is being implemented in several phases. All components and phases together form the Study. Current major components are the Vanguard Study, the Main Study, and Study substudies.

Vanguard Study Versus Main Study. The Vanguard Study is designed to evaluate the feasibility (technical performance), acceptability (the impact on participants, study personnel, and infrastructure), and cost (personnel, time, level of effort, and money) of Study recruitment, logistics and operations, and Study visits and study visit assessments. The outcomes of the Vanguard Study will have a continual and major impact on how the Main Study will be executed. Thus, it is imperative that the Vanguard Study be planned, implemented, and monitored to a level of precision that enables it to serve as a reliable and valid platform to evaluate recruitment, study procedures, visits, scale-up potential, resource requirements, and other aspects for the Main Study.

The Main Study will focus on data acquisition related to effects genetics, environment, growth, and development on the health of children and the analyses of those data for multiple scientific hypotheses. The Vanguard Study and the Main Study have different goals, and the assessment types and assessment techniques used in each of the Study components may be different so there is no intent to categorically merge data among Study components. The Vanguard Study and Main Study will run in parallel, and together with additional Study-funded substudies, will form the composite Study.

Study Terminology. Studies that integrate with the Vanguard Study are funded by the National Children's Study, and focus on a limited question with limited duration will be known as

substudies. Studies that integrate with the Vanguard Study and have independent funding will be known as *supplemental methodological studies*. Studies that integrate with the Main Study and have independent funding will be known as *adjunct studies*.

Study Activity. The Vanguard Study began in January 2009 at two locations. An additional five locations began enrollment in April 2009. The Main Study will begin when there are enough data from the Vanguard Study to responsibly construct the Main Study design. The Main Study start date will be data-based and evidence-driven rather than calendar-driven. The enrollment target for the Vanguard Study will be determined empirically by two factors: (1) recruitment data that indicate a sufficient number of informative events to assess different strategies for scale-up to the Main Study and (2) a cohort size that is adequate to evaluate the Study visit assessments for the duration of the Study.

Current Recruitment Strategy. The goal of the current recruitment strategy is a statistically valid sample that can be generalized to the U.S. population to provide unbiased results and coverage of a broad range of environmental and population characteristics. A statistically valid sample is achieved through demographics of predetermined geographic areas that are divided into segments. All households within a geographic segment are eligible. All women that meet enrollment criteria and live in the household are potentially eligible to enroll in the Study. When a woman becomes pregnant, she is formally enrolled into the Study. The woman must live at an address in an eligible geographic segment when her child is born for the child to be enrolled into the Study.

There are plans to compare three alternate recruitment strategies with the current household-based approach, which will continue re-enumeration in the current seven Vanguard Centers. The alternate strategies are (1) a provider-based strategy in 10 additional locations, (2) enhanced household survey enumeration in 10 additional locations, and (3) high-intensity/low-intensity (HiLo) strategy in 10 additional locations. This expansion will yield a total of 37 locations in the Vanguard Study. The alternate approaches will conduct parallel activities for improved efficiency in evaluation of recruitment numbers, community tolerance, and cost to inform methods appropriate for the Main Study.

Visit Assessments. Visit assessments (those tests and assays administered to Study participants at a visit) can be tested in all current contract sites. The Study Program Office is currently developing a series of analytic criteria. About 250 different visit assessments (environmental samples, biospecimens, measurements, questionnaires, and so on) that are currently in the Study catalog will be evaluated. Each visit has a schedule that may contain questionnaires, physical and laboratory measurements, biological samples, environmental sample collections, or other assessments. For each outcome assessment for each visit, an *a priori* analysis is under way to determine the estimated count of informative events to provide 95 percent confidence limits around the reproducibility of the assessment that will allow an evaluation of whether to scale up with an acceptable standard deviation, modify the outcome assessment and retest empirically, or eliminate the outcome assessment from consideration for the Main Study. Study visit assessments must be feasible, reliable, reproducible, and informative. They must have value, lack redundancy, and be able to address a question that has potentially important public health impact,

requires a study of the Study's size and robustness to answer, and is unlikely to be answered in another context.

Hypothesis Selection. The selection of scientific hypotheses for the Main Study will be guided by the empiric data of the Vanguard Study and other Study-funded substudies, the efforts of the various workgroups and interested parties that proposed and vetted candidate hypotheses, the potential scientific and public health impact, and a perceived requirement to use the Study and not another alternate as the data acquisition platform. All current Study efforts are directed to inform the Main Study with regard to design and elements. The Main Study design will be dependent upon results of recruitment evaluations. All components for the Main Study must have relative value and be scalable.

Main Study Considerations. Main Study recruitment rate estimates based on Vanguard Study empiric data will determine the duration of enrollment to reach the accrual target of 100,000. Main Study cost estimates will be based on study design factors such as duration, effort, and costs for recruitment; geographic location and resource footprint for each visit; scale-up costs of data processing, quality assurance, data archiving, and data analysis; and number, complexity, and costs for outcome assessments. Additional secular factors such as health care, transportation, data security, and other costs will affect the Main Study cost estimates. In general, major cost drivers are recruitment strategy, number of visits, and complexity of each visit. The resource footprint for each visit as well as study operations is largely a function of the number of personnel involved and the level of effort required for data collection.

Study Methodology and Credibility. The Vanguard Study uses established study methodology to recruit pregnant women into the Study. Its infrastructure, directed by the Study Program Office and supported by a nationally recognized data collection and research organization, supports high quality data collection. Vanguard Study protocol procedures are standardized and documented in 10 volumes of the Manual of Procedures (MOP). Field staff across Vanguard Study Centers are trained and certified on the MOP. Limited and specified local variation was encouraged to determine best practices during this Vanguard Study and thereby inform the Main Study. Management and adherence to the Study protocol is managed centrally by the Study Program Office.

The Study Program Office manages submissions to 122 institutional review boards (IRBs) overseeing the Study, Office of Management and Budget (OMB) approvals and quarterly updates, data security and access, and incidents. Combined, the established infrastructure meets or exceeds human subject research protections established by Office of Human Research Protections (OHRP) and data confidentiality regulations established by the Federal Committee on Statistical Methodology. The production of the revised Vanguard Study protocol document codifies these clarifications of the initial protocol based on field experience and Study program direction. Additional oversight is provided by the Study's Independent Study Monitoring and Oversight Committee (iSMOC), the ICC, and the Office of the Director, National Institutes of Health.

Internal consistency is an indicator of reliability of data. The data collected in the Vanguard Study have been internally consistent in that Study Centers are reporting similar values on a Center basis from month to month over the past 6 months. The Vanguard Study data has been externally consistent with other studies.

NCSAC Discussion

- Patricia O'Campo, Ph.D., asked how the current approach to hypothesis selection will affect the original hypotheses. Dr. Hirschfeld explained that the original hypotheses were examples of hypotheses that might be answered by the Study; they were not commitments. The new paradigm is based on the reliability and feasibility of what the Study can execute. The Study will serve as a high-quality data acquisition platform that will allow some hypotheses to be addressed as the Study begins. The Study must maintain the potential to address hypotheses that have not yet been formulated.
- Janet Currie, Ph.D., asked whether the current data access guidelines apply to the Vanguard Study. Dr. Hirschfeld replied yes, current data access guidelines would apply but that each component of the NCS had a different purpose. The purpose of the Main Study is to examine the relationships between environmental exposures and health outcomes. The purpose of the Vanguard Study is to determine the feasibility, acceptability, and costs of visit assessments. Vanguard Study data will inform the operations, costs, and efficiencies of the Main Study and may not be informative with regard to exposures and outcomes and other scientific interests.

Report from the Director's Office, NICHD

Alan Guttmacher, M.D., Acting Director, NICHD, NIH, HHS

Dr. Guttmacher noted his familiarity with the Study and outlined the reasons why he accepted the position of Acting Director, NICHD. First, the various missions of the NICHD align with many of his scientific interests. Second, he knew that the NICHD was the lead agency for the Study. Dr. Guttmacher has been interested in the Study since its inception and understands the Study's potential to have an impact on understanding children's health and development. Good leadership for the NICHD and its contribution to the Study at this time is of great importance. In addition, the Office of the Director, NIH, and other NIH leaders view the Study as important to the NIH's mission. Dr. Guttmacher said he will work to get other NIH Institutes and Centers involved in the Study. Other programs within the NICHD will continue to engage with the Study. Dr. Guttmacher emphasized that the Study is committed to being data-driven. Decisions regarding the Study will be based on data, not assumptions. The Vanguard Study will generate data that will inform the Main Study. The Study is a dynamic study, and it will continue to evolve. The Study should be viewed as a resource and not as a study in the conventional sense. It is not designed to answer specific questions. It is designed to serve as a high-quality data acquisition platform—a resource that can be mined by multiple investigators over the coming years. Data access is an important element of mining Study data. If the Study is a successful resource, it will be able to address future—and currently unimagined—hypotheses. Because of

its uniqueness, the Study has the potential to make a historic contribution to understanding children's health and development.

NCSAC Discussion

- Joan Y. Reede, M.D., M.P.H., M.B.A., said the Study is a resource to engage future researchers. She asked how the Study will bring more children's researchers into its processes. Dr. Guttmacher replied that if a robust and promising resource is created, it will attract the various scientists and researchers who are interested in children's health and development. The Study's cutting-edge science will allow researchers to answer important questions about environmental exposures and health outcomes. Scientists with diverse experience, interests, and perspectives will be needed to fully address all of the Study's potential questions. Dr. Hirschfeld noted the Study's relationship with the Clinical Science Translation Awards (CTSA) consortium. The Study and the CTSA consortium are exploring the needs and opportunities for engaging and training pediatric researchers. NICHD leaders are exploring ways to involve other NICHD consortia and networks with the Study.

General Discussion

- Alan Trachtenberg, M.D., M.P.H. (public participant), asked whether the issue of diversity within the Study sample has been considered and discussed. He said there is a concern among the less numerous ethnic groups—particularly American Indians and Alaskan Natives—about not being adequately numerically represented and not having geographic areas where these ethnic groups reside included in the Study. Dr. Guttmacher explained that the Study is a representative sample that will be statistically valid. Dr. Fleischman noted that the NCSAC has been clear about the potential of adjunct studies to compare other cohorts to the Study cohort.
- Everett Rhoades, M.D., said there is oversampling of certain geographic locations where there are substantial American Indian populations. He noted the Study locations in Arizona and Oklahoma.
- Jonas H. Ellenberg, Ph.D., asked how the Study will get day-to-day input from biostatistics and epidemiologic experts. Dr. Hirschfeld said such input is solicited from the 36 Study Centers. The Study Centers can use subcontractors to help answer certain questions. In addition, workshops are held to address specific questions. The Study seeks a spectrum of input from multiple sources using a systematic approach. There are no limitations to input and no fixed working groups. Allen Dearry, Ph.D., commented that the Study's Scholars Program provides an opportunity for input and collaboration with federal scientists.

Vanguard Study Recruitment and Study Visit Update

Christina Park, Ph.D., Senior Scientist and Study Center Project Officer, NICHD, NIH, HHS

Dr. Park reported on the status of enumeration and pregnancy screening (EPSC), eligibility and enrollment, and pregnancy data collection. As of December 28, 2009, recruitment status was as follows:

Recruitment Stage	Number of Cases	Response Rate
Total listed dwelling units/households	83,152	
Household enumeration completed	63,812	81%
Age-eligible women identified	31,508	
Pregnancy screening completed	27,349	87%
Pregnant eligibles identified	1,000	
Consented/enrolled women	510	61%

As of December 28, 2009, data collection completed was as follows:

Pregnancy Data Collection	Number
Consented/enrolled women	510
First trimester mother visit	93
Third trimester mother visit	154
Prenatal father visit	93
Birth visit	83

As of December 28, 2009, prenatal visit data collection was as follows:

Outcome	T1 First Mother	T3 Prior Mother	T3 First Mother	Prenatal Father
Number eligible	446	153	108	500
Data collection complete	66%	54%	68%	19%
In scheduling stage	15%	37%	20%	60%
Data not collected	19%	9%	14%	21%

Dr. Park summarized recruitment and Study visit findings:

- Response rates at various stages of recruitment are comparable with or higher than those from other large studies.
- Initial assumptions regarding the combined rates from enumeration through enrollment were ambitious (75 percent versus 42 percent).
- Dynamic variability in recruitment that changes weekly is seen among Vanguard locations.
- Enrollment into the Study does not appear to be affected by race/ethnicity or language spoken.
- Younger women are more likely than older women to enroll in the Study.
- Women who had received an advance letter or who had previously heard about the Study were more likely to enroll.

- As of November 16, 2009, 209 women had consented to collection of biologic and environmental samples at the first trimester visit.

NCSAC Discussion

- Dr. Fleischman stated that from his perspective, a 60 percent rate of enrollment consent is extraordinary. He asked Dr. Park to explain the composite participation rate of the household-based recruitment. She explained that the composite rate is the product of the multiplication of the household enumeration rate, the pregnancy screening rate, and the enrollment consent rate. As of December 28, 2009, the composite participation rate was about 40 percent. Dr. Hirschfeld commented that the consent rate had been estimated to be about 70 percent, and the estimated proportion of pregnant women was about twice the current empiric rate. The recruitment and enrollment assumptions were not as robust as anticipated.
- Bruce D. Gelb, M.D., asked whether the composite participation rate is sensitive to the rate of pregnancy. Dr. Hirschfeld said it is not. Dr. Park clarified that the composite rate involves enumeration, pregnancy screening, and enrollment, not the rate of identifying eligible women. Dr. Gelb asked about the expectations for enumeration and pregnancy screening response rates. Dr. Park said these rates were not determined separately.
- David J. Schonfeld, M.D., asked whether the rates were cumulative. Dr. Park said they were. Dr. Schonfeld asked whether there are improvements over time at the Vanguard locations, that is, whether staff knowledge and experience have positive effects. He said all Study Centers might benefit from a run-in phase. Dr. Hirschfeld said there is clear evidence of a learning curve at the Vanguard Centers. Principal Investigators (PIs) have been tracking progress at their Centers. The Study Program Office has developed mechanisms to capture and implement what has been learned at the Vanguard Centers.
- Dr. Reede asked for clarification on the 19 percent of women whose data are not collected in the first trimester visit. Dr. Park explained that about 7 percent are women who move out of the Study segments or who experience pregnancy loss. About 8 percent are women who were missed because the data collection visit could not be scheduled within the appropriate timeframe. Dr. Reede asked whether the data from the 8 percent could be collected later. Dr. Park said these women are eligible for the third trimester visit, and data have generally been collected from them.
- Helen DuPlessis, M.D., M.P.H., asked whether there are enough data to evaluate the relationship between the interviewer type and the type of incentives on outcomes. Dr. Park said there should be enough data, but they have not yet been compiled.
- Dr. Currie noted the low rate of completed prenatal data collection for fathers and asked whether the data could be conducted in hospitals at the time of delivery. Dr. Park said that about 60 percent of the prenatal father visits are in the scheduling stage. Because they are

extensive and involve the collection of environmental samples, the father visits must be conducted in the home and not at the hospital at time of birth.

- Carol Henry, Ph.D., asked about the difference in the data collected in the first trimester and third trimester. Dr. Park explained that the data collected in the first mother visit, whether collected in the first trimester or third trimester, is the same and is more extensive than the data collected in the second mother visit. Sonograms will be conducted during the second trimester.
- Maria Cancian, Ph.D., noted that some father data can be collected at the time of birth, particularly from nonmarital fathers. Dr. Hirschfeld said the Vanguard Centers are exploring alternate data collection from fathers at the time of birth.

NCSAC Recommendations

- Dr. DuPlessis suggested that the Study evaluate the relationship between the interviewer type and the type of incentives on outcomes.
- Dr. Currie recommended that the Study collect paternal data in the hospital at the time of delivery.

Rationale for Additional Recruitment Strategies for the National Children's Study

Dr. Hirschfeld

Overview. The need for additional recruitment experience was anticipated by the Institute of Medicine's (IOM) review of the Study's scientific plan. Current field data suggest that the current household-based recruitment method is not meeting expectations. Systematic data collection and analysis of alternate recruitment strategies would provide a field-tested portfolio to inform the Main Study design and allow greater flexibility in methods to be used in localities. The target date of completion of enrollment for the Main Study can be favorably affected by new strategies compared to continuation of the current strategy.

IOM Report. The report noted that the process of identifying births from a national sample of households is complex and subject to numerous sources of attrition of uncertain magnitude. Because of this, it will be difficult to predict how many households must be initially selected to produce a probability sample of 1,000 births in each of the Study sites. The report recommended the following:

- The Study should consider the proposed household enumeration approach to be experimental and should conduct carefully designed field studies to clearly establish the statistical and practical implications of the proposed adjudicated listing approach.
- The Study should consider modifying the sampling design to allow for flexibility in increasing the number of study participants in the event that the estimated number of screened households needed to reach 1,000 births per primary sampling unit (PSU) is incorrect.

Observed Versus Expected. Initial estimates were that each Study location would have on average about 5 births per week at steady state or about 250 births per year. Steady state means that enough time has passed so that the birth number reaches a plateau, which can be between nine and 12 months after beginning the process. Over 4 years the result would be about 1,000 births per location. For about 105 locations, the result would be a cohort of a few thousand births into the Vanguard Study and about 100,000 births into the Main Study. In the current Vanguard Study:

- About 80 percent of the households have been contacted and enumerated.
- About 50 percent of those households had a woman who meets enrollment criteria.
- About 1–2 percent of the age-eligible women have been pregnant
- About 60 percent of pregnant women enrolled in the Study.

The current enrollment rate would yield about 107 births per Study location per year after steady state is reached; 107 observed over 250 expected is about 43 percent. If the same geographic areas were resampled annually, the assumption in the model is that the number of pregnant women who would agree to enroll in the Study would be about the same unless there was a significant change in women who are referred into the Study by efforts supplemental to the household enumeration. To extrapolate the current household enumeration based recruitment model from the Vanguard Study to the Main Study of about 105 locations, the anticipated enrollment of births would be about 11,000 births per year, or slightly less than about 9 years to reach the enrollment target of 100,000.

Evidence-Based Toolkit. Field testing of alternate recruitment strategies would allow greater precision in designing the Main Study. The current Vanguard Study locations are sufficiently advanced in their recruitment efforts that new Study locations in new geographic areas are necessary to evaluate alternate strategies adequately. The Study Program Office intends to assign 10 new Study locations from the pool of locations currently under contract to examine each of three additional recruitment strategies, for a total of 30 additional locations. The selected strategies are based on review of literature and discussions with experts from the National Cancer Institute, the National Center for Health Statistics, the U.S. Census, and the Department of Education. The ICC and ad hoc consultations have provided additional input.

Target Date for Enrollment Completion. The Study program incorporates both a 21-year Vanguard Study and a 21-year Main Study. The completion date for each study is 21 years after the last child is enrolled. The resource intensive phase of each study is the recruitment and enrollment phase. Once enrollment is complete, each study will have a less resource intensive phase of data acquisition through scheduled study visits. The sooner the Main Study completes enrollment, the sooner the resources required become less intensive and the sooner the collected data are available for analysis and to inform health policy assessments and development. Extending the current Vanguard Study recruitment experience without revision and further testing of alternates to the Main Study is likely to result in a prolonged recruitment phase of up to 9 years. Increasing the Vanguard Study operations systematically and applying the most effective methods given results can favorably affect when the Main Study will complete enrollment. The resources necessary to acquire the additional recruitment and visit assessment data from the Vanguard Study do not represent additional expenditures.

Additional Benefits. Additional benefits include:

- Greater precision in selecting recruitment strategies for the Main Study
- Increased flexibility in allowing for multiple recruitment strategies for the Main Study
- Increased rate of data accumulation due to parallel activities
- More sites with Study experience when Main Study launch begins
- Emphasis on Main Study enrollment completion target date.

Implementation Plans. All work will be performed under current contractors and under the framework of current contracts. The Study Program Office plans to modify contracts of current Vanguard, Wave 1, and Wave 2 sites to perform work related to exploring additional recruitment strategies. Protocol design and Study visit assessments are not changed. Each approach is 4–6 months from concept to field implementation and then 4–6 months to acquire sufficient data for preliminary analyses.

Request for Letters of Intent. The Study Program Office issued a request for Letters of Intent on December 24, 2009. Responses are due on January 20, 2010. Selection is targeted for February 1, 2010. Selection will be based on the scientific, logistical, and operational quality of the proposal, with consideration for factors such as geography and demographics. There is no limitation on the number of strategies an individual Center, including the current Vanguard Centers, may apply for.

The NCSAC was asked to address the following question:

- Does the NCSAC support the rationale for exploring additional recruitment strategies in the context of the Vanguard Study?

NCSAC Discussion

- Dr. Fleischman noted that about 30,000 pregnancy screenings have been completed, 1,000 pregnant-eligible women have been identified, and 500 women have consented/enrolled. He asked Dr. Hirschfeld what these numbers should have been to indicate that the Study's recruitment and enrollment were as anticipated. Dr. Hirschfeld said enrollment should have been about 225 percent greater at this time in order for the Study to complete enrollment of 100,000 participants within the 4-year timeframe.
- Benjamin S. Wilfond, M.D., said recruitment is the most challenging issue for studies. He said he supports the piloting of alternate recruitment strategies.
- Michelle A. Williams, Sc.D., S.M., M.S., said she also supports the alternate recruitment approaches. She noted the importance of collecting placenta data. She proposed that the Study evaluate among the births the proportion that complete each data collection element at each of the prescribed collection times. It is important to know how many women complete the protocol on time.

- Edwin Trevathan, M.D., M.P.H., asked about the extent to which pregnancy rates play a role in recruitment and enrollment. Dr. Hirschfeld said there are not enough data to answer this question.
- Melissa Tassinari, Ph.D., asked what the Study Program Office is doing with the data collected from the current recruitment strategy in terms of maximizing its performance. Dr. Hirschfeld explained that the current Vanguard Centers meet regularly to discuss recruitment and compare experiences. In addition, the Study Program Office meets with Vanguard Centers individually to discuss recruitment performance and explore ways in which recruitment efforts can be augmented. Vanguard Centers are engaged in regional discussions and collective information sharing. Dr. Hirschfeld acknowledged that the Study's messaging may not be as efficient as needed. Because of this, the Study Program Office is reframing the Study's communication plan.
- Dr. Currie asked whether the Study knows the number of births in each segment. Dr. Hirschfeld said there is a lag in the availability of data, some of which are 2 years old. The Study is looking at surrogates to get more up-to-date data on birth rates.
- Michael F. Greene, M.D., asked whether changing the recruitment approach will change the type of people who are recruited into the Study. Dr. Hirschfeld said this issue has been considered and will be analyzed in comparing the three alternate recruitment strategies with the current Study data as well as census data and birth records. Although the Study's goal is a representative sample, the sample will never be truly representative of the U.S. population. As long as the Study collects data that are generalizable and of high quality, it will meet the mandate of the Children's Health Act.

NCSAC Recommendations

- The Committee supports the piloting of alternate recruitment strategies.
- Dr. Williams emphasized the importance of collecting placenta data.
- Additionally, Dr. Williams recommended that the Study evaluate among the births the proportion that completes each data collection element at each of the prescribed collection times.
- Dr. Greene cautioned Study Planners that changing the recruitment approach may change the type of people who are recruited into the Study.

Provider-Based Recruitment

*Ruth Brenner, M.D., Associate Study Director for Science and Director for Study Centers,
NICHD, NIH, HHS*

The first stage of the current household-based sampling and recruitment strategy involved the selection of 105 Study locations in order to create a sample representative of the U.S. population. Study locations are primarily counties. The second stage of sampling involved the selection of segments within Study locations. Segments are comparable to neighborhoods. There are about

1,000 households per segment. Women are eligible for the Study if, at the time of delivery, their household is in a selected neighborhood.

The initial household-based recruitment strategy involves EPSC, household enumeration, and screening of age-eligible women. There is ongoing recruitment through follow-up phone calls, ongoing outreach with subsequent referrals, and selected re-enumeration of households. The household-based approach is challenging because it is labor intensive, particularly in the initial recruitment phase. Early data suggest that participation is lower than initially projected.

In order to improve recruitment, three alternate strategies have been proposed: provider-based recruitment, enhanced EPSC, and a high-intensity/low-intensity dynamic model. There will be no change in the first and second stages of sampling. The target sample is all newborns of women residing in a Study segment during the enrollment period.

Provider-based recruitment will recruit women through health care providers, including obstetricians, family practitioners, public health nurses, pediatricians, midwives, and others. A precedent for this approach was established in many other studies and research networks. One advantage of provider-based recruitment is the initial introduction to the Study by a trusted source. The pilot protocol is designed to evaluate the feasibility of this approach across multiple diverse settings and with multiple diverse populations. The Study Program Office anticipates conducting this pilot in about 10 Study locations.

Potential considerations include participation of providers (for example, the percentage of providers who agree to participate and the specific activities that providers are willing to do). Preliminary work includes outreach to professional organizations such as the American College of Obstetricians and Gynecologists, survey of all Study Centers, and discussions with experts. Most Centers could identify the relevant providers. About two-thirds of providers are willing to participate, but most will not administer informed consent. The provider-based approach may be most useful in rural locations where there are fewer providers.

Other potential considerations include the recruitment and retention of women (for example, the number of eligible women that are identified, the percentage of identified women who agree to participate and the difference of this percentage from other recruitment strategies, the retention rate, variations in recruitment rates by the type of provider activity, and likelihood of participation if Study staff is co-located in provider offices).

A request for Letters of Intent was issued on December 24, 2009. The pilot protocol(s) will be largely driven by the responses received. Centers will need to identify providers of care for women residing in the selected Study segment, work with the providers to identify and recruit eligible women, and determine the capture rate (women recruited/women eligible for recruitment) during the pilot timeframe. This approach takes advantage of the creativity and expertise of the Study Centers.

NCSAC Discussion

- Dr. Reede asked whether there will be differences in how participants are recruited from community health centers compared with hospitals, clinics, or group practices. Dr. Brenner replied that most likely this will be a component of the provider-based recruitment. Dr. Hirschfeld noted that who is a provider has been broadly defined.
- Thomas Ten Have, Ph.D., M.P.H., asked whether there has been any discussion regarding the absence of preterm data such as a sonogram. Dr. Brenner said the provider-based recruitment will focus primarily on prenatal care visits. There has been some discussion about women who do not receive prenatal care. Women can be enrolled in the Study up to the time of delivery. With regard to sonograms, the Study will conduct them at the T2 visits. Providers will also conduct sonograms independent of the Study.
- Dr. Rhoades asked whether provider-based recruitment is coercive, that is, whether women may feel compelled to participate if their provider suggests it. Dr. Brenner commented that providers will be trained to inform and recruit women, but they will not consent and enroll them.
- Dr. DuPlessis said providers such as health education nurses and birthing class leaders should be included.
- Dr. Ellenberg asked whether the provider-based recruitment cohort will come from the existing probability sample. Dr. Brenner said these participants will reside in the previously defined segments.
- Dr. O'Campo commented on the current recruiting strategy. She noted that there are differences in the recruiters who are making phone calls to potential participants; some are more successful than others.
- Dr. Williams said the provider-based recruitment will disproportionately miss women who do not receive prenatal care or who seek prenatal care late in their pregnancy. She asked how the Study will evaluate and plan for the undersampling of women who do not receive prenatal care. Dr. Brenner said women who do not receive prenatal care will be able to enroll at the time of birth. There will still be a large outreach effort and presence in the Study location, and women will be able to self-refer. Women who enroll through provider-based recruitment and their children will be monitored and evaluated for retention.
- Dr. Gelb observed that there will be some bias in the types of women who are recruited through the provider-based approach. He proposed that the Study evaluate this bias.
- Dr. Wilfond said that although there may be some bias, it may not be significant. It may be challenging to evaluate. He commented that provider-based recruitment is not coercive because it does not involve threats. However, trusted figures such as physicians can be influential. The Study could assess patients' perception of influence and feelings of obligation because of a physician's referral.

- Dr. Henry asked why the Study is not increasing the number of households by expanding the segment sizes. This approach would maintain the representative sample. Dr. Brenner said expanding the segment size would not necessarily improve the response rates. One of the goals of the alternate recruitment approaches is to gain knowledge about recruitment processes in general.
- Elena Gates, M.D., said, based on her experience, recruiting women through providers during registration did not work very well because staff are more committed to patient care than to a study. What did work well was getting permission from patients to be contacted by recruiters.
- Michael D. Lebowitz, Ph.D., expressed his concern about generalizability and bias, particularly with convenience samples. He asked whether a statistical analysis has been performed to determine generalizability. Dr. Brenner said the sample and target population have not changed; they are the same as the household-based sample and population. The NCS population is not a convenience sample.
- Dr. Cancian noted that there may be bias in the current household-based approach. The question is whether the alternate recruitment strategies will increase or decrease bias.

NCSAC Recommendations

- Dr. Rhoades expressed concern with the possibility that a provider-based recruitment strategy could be considered coercive. Dr. Wilfond disagreed. Trusted figures may be influential but not coercive.
- Dr. Wilfond recommended that the Study assess patients' perceptions of influence and feelings of obligation because of a physicians' referral.
- Dr. DuPlessis recommended that providers trained to inform and recruit women into the Study should include health education nurses and birthing class leaders.
- Dr. Gelb proposed the Study evaluate the inherent bias of the recruiter-based approach.
- Dr. Henry suggested that the Study increase the number of households by expanding the segment sizes.
- Dr. Gates recommended that the Study ask providers to obtain permission from patients to be contacted by Study recruiters.
- Dr. Lebowitz expressed his concerns with generalizability and bias.
- Dr. Cancian added that Study needs to determine which recruitment strategies increase or decrease bias.

Enhanced Household Recruitment

Sarah Keim, Ph.D., Associate Study Director for Operations and Logistics, NICHD, NIH, HHS

The current household-based recruitment approach has been ongoing since early 2009 at seven Vanguard locations. It is the primary mode of recruitment to date. The household-based approach has used some methods from other studies, whereas other methods are new (for example, the pregnancy screener). The household-based approach offers the possibility of reaching people who would not normally seek out participation. It is one way to meet the goal of

a nationally-representative, probability-based sample. However, it is labor-intensive and people may be challenging to reach.

One of the proposed alternate recruitment strategies is to enhance the current approach using best practices gleaned from experience, additional recommendations from other studies (for example, the National Health and Nutrition Examination Survey [NHANES] and the U.S. Census), and adding new components expected to boost participation. Data collection will proceed as before.

The general goal of enhanced household recruitment is to optimize the household-based approach to ensure that it presents a resource-effective recruitment strategy with predictable performance. The pilot protocol will involve 10 Study locations and begin mid-2010. It will consider the use of alternate strategies to the current approach of each center selecting its own methodology and staff. For example a central professional organization with full-time and experienced staff hired and trained centrally could travel to the Study locations augmented by local personnel with area knowledge.

The enhanced household-based recruitment approach will focus on raising awareness, gaining cooperation, and improving training and equipment.

The Study Program Office is currently requesting NCSAC advice on the approach and plan, receiving feasibility and cost information from Study Centers, and planning implementation. The timeline is as follows:

- Spring 2010—IRB and OMB approval; instrument and infrastructure development
- Summer 2010—initiation of startup activities; outreach and engagement, media
- November 2010—initiation of participant recruitment
- August 2011–November 2011—completion of pilot data collection.

The NCSAC was asked to address two questions:

- What should be the target response rate for the Study locations involved in the household-based approach?
- In selecting Study locations to participate in this approach, what criteria are most important to consider?

NCSAC Discussion

- Dr. Fleischman asked how the enhanced household recruitment differs from the current approach, which will continue to evolve and improve with the Vanguard Centers' experience. Dr. Keim explained that there are now data from the Vanguard Centers about community outreach, community engagement, and recruitment activities. The Study Program Office has been evaluating the data to determine which activities have been most effective. The enhanced household approach will use best practices and implement them in a more consistent and more focused manner. The data can be used to inform other studies.
- Dr. Schonfeld said the alternate recruitment approaches explore techniques that motivate behavioral change and will consequently increase interest in the Study. He noted that there is

a large body of science in advertising and marketing. There is expertise in these and other fields on how to reach target audiences. Resources could be used strategically to use this expertise.

- Dr. Hirschfeld said there is a difference between the Study and the marketing of a product or requesting episodic engagement in a study such as the NHANES. Study participants are asked to make the Study part of their lives for about 25 years.
- Dr. Wilfond asked whether the Study is examining ways to improve initial enumeration and screening. Dr. Keim said the Study is refining enumeration and screening procedures by shortening and simplifying them. Data collectors have been providing feedback on how to refine the procedures.
- Dr. Fleischman asked whether the Requests for Letters of Intent include better understanding of community engagement in the alternate recruitment strategies. Dr. Keim said community engagement is a core element of the strategies.

NCSAC Recommendations

- Dr. Fleischman emphasized the importance of community engagement while implementing and evaluating the various recruitment strategies.

Vanguard HiLo: A Pilot Study of a High-Intensity/Low-Intensity Dynamic Model for Recruitment

Brian Haugen, Ph.D., Senior Scientist and Study Center Project Officer, NICHD, NIH, HHS

The goal of this alternate approach is to design, implement, and test a recruitment and data-collection model using a mix of low-intensity and high-intensity methods. “Intensity” refers to the level of effort and resources applied by Study staff and infrastructure (cost) and the burden experienced by Study participants and Study infrastructure (acceptability and feasibility). This alternate recruitment plan involves a two-cohort strategy: high-intensity participation with visits and low-intensity participation with survey instruments. Examples of the HiLo approach include the U.S. Census short form and long form (prior to 2010), the Canadian Longitudinal Study of Aging, and the Multi-Ethnic Cohort Study of Diet and Cancer.

The low-intensity study cohort will be recruited through marketing, direct mail, and other referral techniques. The low-intensity study will enroll participants from a broad-based population beyond the predefined geographic segments, such as complete zip codes. Participants will receive Web-based, mail-in, or telephone-based brief questionnaires on a periodic basis. Size will be dependent on the high-intensity study cohort.

The high-intensity study cohort will be drawn from the subset of low-intensity study participants that live in the predetermined geographic segments of the Primary Sampling Units (PSUs). New participants from the low-intensity pool will be added dynamically, as participants leave the high-intensity study or decline further participation. Subpopulations that may have higher

attrition rates or have other characteristics of interest may be oversampled. Data collections follow the planned visit schedule implemented in the first seven Vanguard Centers, including home and clinic visits. The target cohort size for the high-intensity study would be 100,000, so the low-intensity study cohort would be larger than 100,000.

The HiLo approach improves community tolerance for the Study, decreases immediate privacy issues associated with enumeration and enrollment, provides Study resiliency to attrition and nonresponse, allows increased opportunity for testing items, and increases efficiency of recruitment.

Primary objectives of the HiLo protocol are to address the following questions:

- Can low-intensity methods enroll a large percentage of the eligible population within a defined geographic region?
- Do participants participate reliably in low-intensity data collections?
- Do participants in the high-intensity study participate reliably in high-intensity data collections?
- Are HiLo participants retained in the Study effectively?
- Do HiLo participants become pregnant and enroll their babies at sufficient rates?

Other objectives are to refine Study assessments used in the initial seven Vanguard Centers, test low-intensity data collection instruments, and test alternate high-intensity study assessments.

The Study Program Office is currently requesting NCSAC advice on the approach and plan, receiving feasibility and cost information from Study Centers, and planning implementation. The timeline for HiLo implementation is as follows:

- Spring/summer/fall 2010—IRB and OMB approval; instrument and infrastructure development
- November 2010—initiation of startup activities; outreach and engagement, media
- February 2011—initiation of participant recruitment
- August 2011–November 2011—completion of pilot data collection.

The NCSAC was asked to address two questions:

- What should be the target ratio of size for high-intensity/low-intensity cohorts?
- What should be the target response rate for the regions targeted for low-intensity study?

NCSAC Discussion

- Dr. O'Campo asked whether the HiLo recruitment strategy will be conducted within the existing Study locations. Dr. Haugen clarified that recruitment of the low-intensity cohort is not restricted to the predetermined geographic regions. However, to be included in the high-intensity cohort, women must reside in the Study segments. The high-intensity cohort will be recruited from the low-intensity cohort. There may be randomization of selection into the high-intensity cohort. The intent of the Study, however, is to enroll all pregnant women who reside in a segment.

- Dr. Ten Have commented that the HiLo strategy could be subject to the same type of bias issues as the other alternate recruitment strategies.
- Dr. Fleischman asked whether the Study will inform women that they are in either the high-intensity or low-intensity study. Dr. Haugen said the women may not be informed; the distinctions between high-intensity and low-intensity may not be made. The women will be informed that there are different levels of participation in the Study and that there is a selection process.
- Dr. Gelb asked why the low-intensity cohort is needed (that is, what questions can the cohort answer that the high-intensity cohort cannot). Dr. Hirschfeld said the HiLo approach provides an opportunity to rethink the nature of the Study’s questions and hypotheses. There is also an opportunity to frame the questions that will be asked in the low-intensity cohort.
- Dr. Wilfond asked whether the general cost of the HiLo approach has been estimated and how it compares with the cost of a U.S. Census for a fixed population. Dr. Hirschfeld replied that a meeting with U.S. Census representatives is planned for February.
- Dr. Schonfeld said individuals from the low-intensity cohort could be used to “backfill” the high-intensity cohort when women drop out. But the only way to be in the high-intensity cohort is if women live in Study segments. Given the current low rate of participation, there may not be enough women in the low-intensity cohort for the backfilling. In addition, if women are given the opportunity to opt out, the high-intensity cohort may decrease. Because it does not require interviews or biospecimens, the low-intensity study will probably not be costly and recruitment could potentially be completed in 2–3 years. Dr. Hirschfeld said the Study is not locked into the 4-year recruitment timeframe. The alternate recruitment strategies could yield a more efficient timeframe.

NCSAC Recommendations

- As with the other recruitment strategies, some Committee Members were concerned with the possibility of the HiLo strategy introducing bias.
- Dr. Schonfeld suggested that individuals from the low-intensity cohort could be used to “backfill” the high-intensity cohort as women drop out of the Study.

General Discussion of Alternate Recruitment Strategies

- Dr. O’Campo asked how the Study will evaluate and compare the alternate recruitment strategies. Dr. Keim said a number of metrics will be used, including the number of live births, costs, and consent rates. Dr. Brenner said the data may be able to determine who is in the Study versus those who should be in the Study.
- John L. Butenhoff, Ph.D., asked whether the Study will use resources to target nonrespondents (that is, the alternate recruitment strategies would be augmented with door-

to-door efforts). Dr. Hirschfeld explained that the alternate strategies will be implemented and evaluated independently and not combined.

- Dr. Cancian commented that knowing who the Study is recruiting and enrolling and who it is not is critical. Knowing the points of comparison is also critical. Alternatives to birth data should be considered.
- Nigel Paneth, MD, M.P.H., a Study Center investigator, said a critical issue in comparing approaches is not just the fraction of the population the Study is capturing but the timeliness of capturing participants. For example, the Study is capturing about 40 percent of pregnant-eligible women in a Vanguard Study location, but only a fraction of these women are being captured in the first trimester. The Study should pay attention to the timing of data collection.
- Dr. Ellenberg asked whether the HiLo approach is being assessed as a recruitment option or as an adjunct study. Dr. Haugen said it is a recruitment option.
- Dr. DuPlessis expressed her concern about the HiLo strategy and whether there is a benefit to individuals in the low-intensity cohort. Simply providing feedback might not be enough to give the individuals a sense of real benefit. Divulging segment boundaries may not pose a privacy risk and may actually improve engagement and recruitment.
- Dr. Tassinari asked whether enhanced household recruitment is an alternate recruitment strategy or whether it is an effective application of lessons learned. It may not truly be a different approach.

NCSAC Recommendations

- Dr. Cancian emphasized the importance of knowing who the Study is recruiting and enrolling as well as knowing the points of comparison. Alternatives to birth data could be considered.
- Dr. Paneth, a Study Center investigator, advised the Study to monitor the timing of data collection (for example, first trimester).
- Dr. DuPlessis suggested the study make public the segment boundaries in an effort to improve engagement and recruitment.

Recognition Ceremony

The following individuals who are ending their tenure as NCSAC members were recognized for their hard work and contributions to the Study: Dr. Butenhoff, Dr. Currie, Dr. DuPlessis, Dr. Gates, Liliana J. Lengua, Ph.D., Amelie G. Ramirez, Dr.P.H., and R. Gary Rozier, D.D.S. Dr. Fleischman was given a plaque in recognition of his service as NCSAC chair.

Data Access for the National Children's Study: Current Plans and Pending Issues

Jennifer Park, Ph.D., Senior Scientist and Study Center Project Officer, NICHD, NIH, HHS

Overview. Sharing Study data is an expectation, a necessity, and a priority. Sharing must be done in a way that preserves the integrity of the data, the privacy of the participant and his/her community, and transparency of study operations. The Study has developed a management structure and policies to support these goals, and work toward these objectives is progressing. The Study Program Office is actively engaged in learning best practices from other studies. Dr. Park discussed considerations, current plans, and pending issues for electronic data access; specimens and samples access; data access/sharing with Study participants; and data access/sharing with communities.

Electronic Data File Access. Prompt access to data is required to answer scientific questions put forth in the Children’s Health Act. Access must be clearly established for all members of the research community. The Study design will present challenges to the protection of sensitive (identifiable) data. Preserving data integrity is vital.

Under its current plan, the Study will make final data files available to all researchers, regardless of Study affiliation. There will be no early access to final data files for Study investigators. There will be no “shadow data” collection nor will its use be permitted (including “extra” specimen collection at localities). This policy ensures equitable access to data, ensures monitored access and use of data, and prepares standard data sets for different purposes. The purpose of the dataset determines the extent of disclosure review and degree of data coarsening and suppression.

Pending issues include (1) expanding data access options available to researchers (for example, through data use agreements, research data centers, and image/audio archives); (2) developing a Web-based data access request tool; and (3) synchronizing tracking tools used for data access, disclosure review, and scientific review for transparency, ease of use, and parsimony.

Specimens and Samples Access. The guiding principle for access to specimens and samples is maximizing the potential use of finite materials. Use of finite materials must balance between investigations for proximal or short-term outcomes (such as perinatal event analysis) and later outcomes; ensure adequate samples for future, as yet unrecognized, analyses; and gain efficiency and utility from ongoing advances in analytic technology.

Under its current plan, the Study will minimize immediate analyses on total Study population. The majority of specimens will be stored in a repository. Specimens and samples will be processed, aliquoted, and stored. The primary focus will be on nested case-control studies. Requests for data access will be handled by the Chair of the Data Access and Confidentiality Committee. Requests for specimens and samples will be reviewed by the Sample Oversight Group.

Pending issues include continuous evaluation of collection feasibility and costs, processing, stability, and prioritization among planned tests.

Data Access/Sharing with Study Participants. Study data will be gathered from participants through the informed consent process. The consent process is designed to tell participants what

the Study would like to collect, why, how the Study would collect it, how the Study would protect it, and when and how the Study can give participants individual test findings.

Personal health information may be important to participants even if tests are conducted sometime in the future. Some tests for the evaluation of samples are known at the time of collection, whereas others are not yet determined. Some tests require lab analysis, whereas others can be reported immediately. Some tests could inform current medical care, whereas others have unknown implications. The ease and salience of analysis for these tests can change over time.

Through the informed consent process, the Study will identify test results that can be reported during the visit and report those findings to the participants. The Study will inform participants that other tests have not yet been determined, and those results will generally not be reported to them. The Study will advise participants that the Independent Study Monitoring and Oversight Committee (iSMOC) will review the testing process over time and make further determinations of how and when additional results could be reported to participants.

As its protocols are refined, the Study will identify those tests that are likely to be conducted by the Study. Among those tests, the Study identifies those with a well-understood evaluation process, time period, and critical values. The Study will prioritize among these tests to determine those that should be analyzed in a short timeframe and reported.

Data Access/Sharing with Communities. Study data will be of interest to communities. Certain research topics may be of particular interest to the locality. A strong rapport with communities is integral to successful study recruitment and enrollment. Communities should be informed that the sample was not designed to produce estimates that are representative of specific geographic communities or states; such estimates may be misleading. There is a potential for disclosure risk.

Under the current plan, Study Centers are encouraged to work with their community advisory boards (CABs) to identify topics of local interest that may be addressed using Study data. These topics are developed into research plans, with CABs providing input into the design. Analyses are conducted by Study Centers in alignment with Study sampling, data access, confidentiality, and publication guidelines. Materials are written for an intended audience and do not replace other investigator-led projects.

Pending community issues include receiving feedback on proposed plans from Study Centers and their CABs, developing an exemplar to initiate this feedback and refine procedures, and developing plans for a Study Annual Report to Participants, which would summarize national findings on selected indicators.

Summary. The many uses of Study data include aggregated national data for analytic purposes by investigators and researchers, individual health data of interest to participants, and aggregated local data of interest to communities and to the nation. The intended purpose and intended user of the data will inform the data access decision making process. The Study's principles of equity, integrity, and transparency guide its data access policy.

NCSAC Discussion

- Dr. Currie noted the following language in the Data Access Manual about maximizing data access to the research community: “This principle pertains to all forms of NCS analytic data.” The types of data are listed. The Data Access Manual then states that the principle does not pertain to Vanguard Study data. Dr. Park explained that it is important to not make the Vanguard Study data widely available because the data will not be carefully cleaned for exposure response analysis. The data will not be packaged for wider data analysis. It will be streamlined. The data will only be used to determine the feasibility, acceptability, and cost of the Vanguard Study. The greater level of cleaning and packaging will be necessary for the Main Study data. The Vanguard Study cohort is not a representative sample. Dr. Currie said that once the Vanguard Study is expanded to 37 Study locations, there may be 2,000 babies enrolled, and the data may be of use to some researchers at some point. Dr. Park said the Vanguard Study will not be made available exclusively to the Study Centers but should be generally available. Researchers may request data through the Study’s Data Access and Confidentiality Committee. She agreed that the language in the Data Access Manual can be improved and should be revised. Drs. Currie and Cancian volunteered to help revise the language.
- Dr. Schonfeld asked for clarification of the meaning of “final data set.” Some of the initial analyses can be important in evaluating the quality of the data. The data should be released for some initial analyses. Dr. Park said the Study Program Office, Study Centers, Coordinating Center, and other contractors will evaluate, clean, and document the data. When data from all Study Centers for a given period of time are packaged into a complete data file, they will be released. There will be standardized data cleaning, processing, and packaging.
- Dr. Schonfeld commented that there are special issues regarding review and release of tribal data. Dr. Park said the Study Program Office has been consulting and collaborating with American Indian and Alaska Native nations and tribes. The Study has been working to build trust among the nations and tribes involved in the Study. The Study has also been consulting with the Indian Health Service.
- Dr. Rhoades commented on his experience with the Strong Heart Study and issues of consent, data gathering, data use and release, and protections of individuals and groups with regard to American Indians and Alaska Natives.
- Dr. Park said she would review the language in the Data Access Manual regarding the release of findings from American Indian tribes. The important message is not only the sensitivity to the Native American communities. The message is that communities have concerns. The Study needs to be sensitive to the impact of the release of findings to communities.
- Alan Trachtenberg, M.D., M.P.H., said tribes do not want to necessarily prevent the release of findings. They are concerned with how the findings are described.

- Dr. Henry expressed her concern regarding (1) informing participants that other tests have not yet been determined and not reporting those results and (2) advising participants that the iSMOC will review the testing process over time and make further determinations of how and when additional results could be reported to participants. She said participants should be informed when their samples are used and that results should be made available. She proposed reviewing and revising the language about reporting results to participants. Dr. Park said the language will be reviewed and revised as necessary.
- Wilma Brakefield-Caldwell, R.N., commented that findings on paternity should not be released.
- Dr. Currie commented on the use of geographic identifiers. Data could be reported at least on the state level. Dr. Park said the restricted use data files will have detailed address information. There are mechanisms to protect information regarding segments from the general public and maintain the confidentiality of the segments. She said there has been no discussion of how non-Study researchers would be subject to site visits.
- Dr. Hirschfeld clarified that Vanguard Study data on feasibility, acceptability, and cost will be made available. He noted that both Study data access policies and NIH data access policies are evolving.
- Dr. Fleischman confirmed that the NCSAC in general agreed with the following:
 - There should be equal data access to all potential investigators regardless of Study affiliation.
 - When Study data are merged with other data sets, the stricter data access policy of all applicable policies has precedence.
 - The Study should consider aligning with other specific data sets for further analyses.

In response to a comment from Dr. Ellenberg regarding publications, Dr. Park explained that the Study's publication policies and data access policies are evolving to improve consistency.

- Dr. Fleischman asked for clarification on the prohibitions of "shadow" data records and specimen banks. Dr. Hirschfeld explained that research in a clinical setting sometimes collects shadow data (that is, "on the side"). The Study prohibits parallel data collection processes and parallel specimen collection processes. This prohibition does not prevent the collection of data in adjunct studies during the Main Study.

NCSAC Recommendations

- Dr. Currie advised the Study to clarify the Data Access Manual language regarding maximizing data access to the research community.
- Drs. Rhoades and Trachtenberg expressed concern with how Study findings are shared with American Indian and Alaska Native populations.
- Dr. Henry was concerned with the Study's approach for reporting test results and the review of test results by the iSMOC. She felt participants should be informed when their samples are used and results should be made available.

- The Committee supports the Study's approach to provide equal access to all potential investigators regardless of Study affiliation.
- When Study data are merged with other data sets, the stricter data access policy of all applicable policies has precedence.
- The Study should consider aligning with other specific data sets for further analyses.

Overview of the Federated Model for IRB Review of the Vanguard Study

Julia Slutsman, Ph.D., Study Bioethicist, NICHD, NIH, HHS

Current Approach. Under the current approach to IRB review of the Vanguard Study, the Study Program Office submits the protocol, amendments, and other supporting material to the NICHD IRB. The NICHD IRB reviews the protocol and amendments, and once they are approved, the Study Program Office submits them to local PIs and IRBs at Vanguard Center for review and approval. Vanguard Center IRBs send protocols to subcontractor IRBs and hospital/birthing center IRBs for review and determination of engagement. The current system for IRB review of the Study protocol involves 7 Vanguard Centers and more than 21 hospital/birthing center IRBs.

All IRBs have approved the initial protocol and subsequent amendments, although with great variability in the time required. All IRBs have made the determination that the Study is minimal risk. Multiple Vanguard Study PIs have voiced concerns about the amount of time, effort and money spent on multiple IRB submissions and communications with local IRB(s). The majority of submissions have been protocol amendments describing minor changes to approved research. Such changes have no impact on risk/benefit ratio and welfare of participants. There is variation in local IRB practices with respect to review of minor changes to approved research. There have been some delays in implementation of Study visits due to time involved in IRB review. There is Study fatigue among some local IRBs due to the large number of amendments and submissions (about 26 during the past year). There is interest among some Vanguard Center institutions in relying on the NICHD IRB.

The Federated Model. The mission of the Federation of Study IRBs is to maintain the highest ethical and regulatory standards in the review and oversight of the Study while minimizing duplicative effort among IRBs across multiple Study locations. The federated model is a mechanism for establishing a shared set of principles, process, and performance for the review of the Study protocols; sharing information across all IRBs; and providing the opportunity to facilitate local IRB review by allowing a reliance on the NICHD intramural IRB. All IRBs required to review the Study protocol are potential participants in the Federation of Study IRBs. Local IRBs at Study locations may select from various tiers of participation and may choose to rely on the NICHD IRB. The Federation is administratively supported and coordinated by the Study Federation IRB Operations Center. The Federation of Study IRBs is modeled after an approach to centralize review for multisite studies first articulated by institutions receiving CTSA's. The federated model was presented to the Secretary's Advisory Committee on Human Research Protections during its July 21, 2009 meeting. This model of IRB review of multisite studies will be implemented as a pilot effort with institutions participating in the Study as well as

the possibility of additional institutions with CTAs participating in pediatric clinical trials. The model will operate through trust, flexibility, coordination, and communication.

Compact for Federation. The Compact for Federation of Study IRBs is a statement of commitment to shared principles, operational process, and measurement of performance in the human subject protections review of the Study Vanguard Study protocol.

The principles of the Compact are as follows:

- Compliance with pertinent regulations
- Commitment to protection of human subjects
- Commitment to focus review on issues most pertinent to the protection of human subjects
- Commitment to ensure that the most up-to-date information and Study documents have IRB approval
- Requirement for procedures describing the withdrawal of individual participants and for closure of the Study, regardless of the risk profile of the Study
- Recognition that outcome measures and assessments should be population specific
- Recognition that assessment schedules should accommodate families and should be age appropriate
- Recognition that local experience should be an important factor in risk determinations made by scientific review groups and IRBs
- Recognition that data sharing is a goal and that the permission, assent, and consent processes should anticipate future uses of data and specimens
- Recognition that variations are possible when determining under what circumstances permission, assent, and consent are required and when they can be waived
- Recognition that demonstrating respect for participating communities by sharing relevant Study results is a goal of the Study
- Recognition that monitoring is context dependent
- Recognition of a hierarchy of evidence in making inferences, extrapolations, and interpreting data
- Commitment to protection of community.

Performance of the Compact is as follows:

- Logistics of protocol distribution from the protocol development team will be handled by a Protocol Coordinator at a Protocol Operations Center.
- IRB review will follow scientific review.
- For initial review of a study, the first IRB will review in one cycle based on regularly scheduled meetings.
- IRB summary review of the initial IRB review will be attached to the protocol package for delivery to subsequent IRBs.
- Subsequent IRB review of a study already approved by a recognized IRB within the Federation will occur in one cycle based on regularly scheduled meetings. Review may be abbreviated.
- Each subsequent IRB summary review will be attached to the protocol package for delivery to the Protocol Coordinator to maintain a composite file of all comments.

- Any changes in perception of risk category or approvability will be communicated to all IRBs by the Operations Center Coordinator upon receipt of assessment.
- Protocol amendments will follow the same process of initial IRB review and subsequent distribution to other IRBs.
- Tracking of time from submission to distribution to action will be warehoused by the Protocol Operations Center.

The process of the Compact is as follows:

- Affirmation of the Federation of Study IRBs Compact and, for those institutions interested in a reliance of facilitated review option, the creation of a Memorandum of Understanding.
- Local experience should be an important determinant of risk so data regarding local experience with assessments and interventions should be available. Absent adequate local data, literature should be used to guide risk determination.
- Criteria for supplemental monitoring such as a recommendation for an Independent Data Monitoring Committee should be proactively developed.
- A common plan between relevant parties such as investigators, institutional offices, sponsors, funding organizations, and regulatory authorities should be proactively developed.
- Information regarding other competent assessments of a proposed study, for example other IRBs or review groups, should be shared.
- Definitions of responsibilities among review parties such as Scientific Review Group, Independent Study Monitoring Oversight Committee (iSMOC), and IRB are clarified.

The advantages of the Federation vary depending on the level of participation an institution accepts. As a central goal of the Federation of Study IRBs, there will be a reduction in duplication of review and a reduction of administrative burden at the local level while maintaining the highest standard of human subject protections review and oversight. Attention to local context is maintained and becomes the priority of the IRB. A mechanism to provide local context is set up between local institution/IRBs and the Operations Center. With less responsibility to provide a duplicative review at the local level, approval turnaround is anticipated to improve. The Federation will establish a culture of information sharing and trust. The next steps for implementing the Federation are to request input from Study stakeholders, the OHRP, and leadership and to coordinate with the CTAs Federated IRB Pilot Project.

NCSAC Discussion

- Dr. Fleischman asked whether any of the Vanguard Centers had developed cooperative research agreements with their IRBs. Dr. Slutsman said many of the hospital IRBs have determined that because the hospitals are not engaged in research, IRB review is not required. Some hospital IRBs have deferred to the Vanguard Center IRBs. The use of cooperative agreements among the Vanguard Centers varies.
- Dr. Fleishman noted that the NICHD IRB is at the core of the Study IRB review process. The NICHD IRB's relationship with the OHRP is different than the relationship between an academic institution and the OHRP. The NIH has a history of arguing about the jurisdiction of the OHRP over NIH IRBs and the relationships among those organizations. Dr. Hirschfeld

said this account is historically correct, but the NIH is moving into a new stage in its interactions with the OHRP. A former NIH official is now director of the OHRP. Dr. Hirschfeld said a key element of the federated model is the addition of an operations center.

- Dr. Fleischman commented that the CTSAs are interested in the federated model. Some of the academic centers have asked the OHRP for new regulations or laws to clarify responsibility and liability for research.

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I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

02/27/10

Date

A handwritten signature in cursive script, appearing to read "Alan R. Fleischman", is written over a horizontal line.

Alan R. Fleischman, M.D.

Chair

National Children's Study Federal Advisory Committee